REMARKS

Applicants respectfully request reconsideration of the present application in view of the foregoing amendments and in view of the reasons that follow.

Claims 1 - 84, 90, 94 - 100, 106, 110, and 113 - 115 have been cancelled during the course of prosecution in this application without prejudice or disclaimer. Applicants reserve the right to file any unclaimed subject matter in one or more continuing applications. Claims 85, 91, 101, 107, 111 and 112 are currently amended. Claims 116 - 135 have been added. This amendment is fully supported by the originally-filed application, i.e., paragraph bridging page 9 - 10, and original claims 2, 3, 4, 41, 49 and 50.

Claims 85 and 91 have been amended to clarify the claimed myristoylated peptides are 10 to 50 contiguous amino acids beginning at the N-terminal glycine of SEQ ID NO: 4. Support for the term "reducing" is found on page 10, lines 3-6 of the specification. Applicants submit that this claim language also is supported by original claim 49, the specification and by known properties of myristoylated proteins. Additional support for this amendment is found on page 9, lines 26-33 and page 12, lines 8-15 of the present specification.

New claims 116-121 are supported by the specification on page 9, lines 31-33. New claims 122 – 135 are supported by pending claims 87, 103, 111 and 112 (the latter two claims prior to the previous amendment) and by the specification on pages 2, lines 6-13 and 17, lines 1-20.

A detailed listing of all claims that are, or were, in the application, irrespective of whether the claim(s) remain under examination in the application, is presented, with an appropriate defined status identifier. After amending the claims as set forth above, claims 85-89, 91-93, 101 – 105, 107 – 109, 111, 112, and 116 - 135 are now pending in this application. No new matter has been added. Applicants acknowledge the withdrawal of the rejections of claims 77-90 and 95-106 based on indefiniteness.

I. The presently claimed invention is supported by the written description

Claims 78-80, 82, 85-89, 91-93, 95-97, 99-109 and 111-115 are rejected under 35 U.S.C. § 112, first paragraph as allegedly failing to comply with the written description requirement because the Examiner states that applicants were not in possession of the full scope of invention.

A. Alleged Ambiguity of the Structure of the N-terminal myristoylated peptides

The Examiner states that the claims are ambiguous because the she considers the phrase "from about" as recited in the rejected claims to be ambiguous because of two possible interpretations of the phrase " a myristoylated peptide fragment of the N-terminal region of the MARCKS protein consisting of **from about** 10 to **about** 50 contiguous amino acids beginning from the N-terminal glycine residue of the MARCKS protein as shown in SEQ ID NO: 4." The Examiner states that "the extent of the N-terminal region of the MARCKS protein remains ambiguous." The Examiner further refers to the Parikh Declaration that she states shows that the first 10 amino acids of the MARCKS protein are essential to mucus inhibition, and states that there was no evidence that other fragments of the N-terminal region of the MARCKS protein that do not contain this minimal sequence would function in mucus inhibition.

In response to this rejection and comments by the Examiner, applicants have amended claims 85 and 91 to clarify the structure of the N-terminal myristoylated peptide so that it is clearly recited the claimed peptide is "a N-terminal myristoylated peptide consisting of an amino acid sequence of from 10 to 50 contiguous amino acids that is identical to a contiguous sequence of amino acids beginning at the N-terminal glycine residue of the MARCKS protein as shown in SEQ ID NO:4." This definition of the peptide makes it clear that 1) the peptide is N-terminally myristoylated; 2) the peptide begins at the N-terminal glycine in the MARCKS protein as shown in SEQ ID NO:4; and 3) the peptide's length is as short as 10 contiguous amino acids but can be as long as 50 contiguous amino acids beginning at the #1 amino acid glycine in SEQ ID NO: 4. Applicants submit that the new claim language provides a clear definition of the structure of the N-terminal myristoylated peptide that is recited in claims 85 and 91, and it is requested that this

rejection for lack of written description be withdraw in view of these comments and claim amendments.

B. MANS Peptide

The Examiner states that the claims that recite "MANS peptide" should also recite the SEQ ID NO:1, because there is no other sequence given in the specification as filed that defines MANS peptide. Although applicants submit that the claims should be read in view of the disclosure and that the skilled person would know that the MANS peptide is SEQ ID NO:1..\ However in an effort to expedite prosecution, applicants have amended claims 101 and 107 to recite "wherein said MANS peptide consists of a N-terminal myristoylated peptide of SEQ ID NO:1." Applicants believe that these claim amendments should overcome this rejection and it is requested that this rejection be withdrawn.

C. Claimed Ranges of the N-terminal myristoylated peptide

The Examiner states that the range "from about 10 to about 20 amino acids" is not supported by the present specification or claims as originally filed. Claims 113 – 115 have been canceled without prejudice and replaced with claims 116 – 121, which applicants submit have explicit basis in the specification on page 9, lines 31 and 32 which recites that "active MARCKS protein fragments are typically at least about five, ten, fifteen, twenty and twenty-five amino acids in length....." In view of the cancellation of claims 113 - 115 and the explicit support provided for the language of new claims 116 – 121, it is requested that this rejection be withdrawn.

Applicants submit that all of the claims comply with the written description requirement, and that the specification describes the invention in sufficient detail that a person skilled in the art could conclude that the present inventors had possession of the claimed invention. Applicants respectfully request that the Examiner reconsider this rejection based upon the arguments and presently pending claims, and withdrawn this rejection.

II. The presently claimed invention is enabled for the full scope of the claimed invention

Claims 78-80, 82, 85-89, 95-97, 99-109 and 111-114 are rejected under 35 U.S.C. § 112, first paragraph as allegedly not being enabled for the full scope of the claims. To support this rejection, the Examiner states that while she considers the specification enabling for inhibiting mucus secretion *in vitro* and for decreasing mucus hypersecretion *in vivo* via airway administration of the MANS peptide or active fragments thereof comprising at least the first 10 amino acids of the MANS-peptide in a mouse model of asthma, she does not consider the specification enabling for the *in vivo* therapeutic treatment of bronchitis, cystic fibrosis, chronic obstructive pulmonary disease comprising administration of the compounds of the present invention.

As discussed above, claims 85 and 91 have been amended to clearly define the active peptides that are encompassed by the claims, and therefore, overcome any suggestion that undue experimentation is required to practice the present invention as claimed because a skilled person reviewing the specification would know which peptides are encompassed by the presently pending claims.

The Examiner comments that applicants' arguments and the Rogers Declaration filed on June 7, 2006, rely upon data submitted in post-filing references to support the assertion of full enablement of the present invention which claims priority back to February 20, 2000. Applicants refer the Examiner to a further clarifying declaration of Dr. Duncan Rogers (Attachment A), attached herewith, where he explains in paragraphs 4 and 5 of his declaration that in his opinion the experimental data produced in these cited references were produced using the guidance from the specification of the present application. Particularly, the Li *et al.* publication disclosed similar experiments in which MARCKS protein involvement in mucus secretion was demonstrated in normal human bronchial epithelial cells (NHBE cells). The studies in Li *et al.* demonstrate that MANS peptide inhibited mucus secretion in a concentration dependent manner as disclosed in the present invention. It is submitted that many inventors publish results in scientific publications that have formed the basis of an earlier filed patent application. In fact, in many instances, such post-published scientific publications are utilized as further evidence of enablement of the present invention similar to data presented in 132 declarations. The present

invention disclosed that MARCKS protein-related mucus hypersecretion can be reduced by a N-terminal myristoylated MANS peptide and fragments thereof. Li *et al.* was a later publication by the same inventors that provided additional data and comments in this specific area.

Similarly, the Singer *et al.* publication discloses additional data in a known animal model that supports that MANS peptide inhibits mucus hypersecretion. In the first column on the first page of Singer *et al.*, the Li *et al.* publication is referenced for the positive results of its *in vitro* data showing that MANS peptide inhibited mucus release in a concentration-dependent manner. Singer then states that MANS was tested in a well-characterized *in vivo* model. Applicants submit, and Dr. Rogers' declaration concurs, that the mouse model was a well known model that was used at least as early as 1995, as evidenced by the Eum *et al.* publication, and that its use to study the effect of MANS peptide and its fragments on mucus hypersecretion was guided by the present invention. The specification of the present invention discloses treatment of diseases in which mucus hypersecretion is a major clinical symptom. As commented on by Dr. Rogers in paragraph 5 of his attached declaration, the data presented in the *in vivo* model in Singer *et al.* is a logical process followed by skilled persons to determine the effectiveness of therapeutic compounds from *in vitro* results to *in vivo* results. He further comments particularly that it was his opinion that experiments in Li *et al.* and Singer *et al.* were guided by the disclosures in the specification of the present application which showed the utility of the MANS peptide and its fragments to inhibit mucus hypersecretion. Thus, applicants submit that the specification provided the guidance for these later publications where the inventors where also co-authors. The present invention discloses that MANS peptide and its fragments are useful to reduce mucus hypersecretion in the airways of a subject and discloses methods of administering the same for reducing mucus hypersecretion in these subjects. Therefore, applicants submit that the Li *et al.* and Singer *et al.* publications provide experimental data that is guided by the present application.

The Examiner also cites the Rogers and Barnes publication from 2006 as a post-published paper relied upon by Dr. Rogers in his previously submitted declaration on June 7, 2006. But this publication was cited by Dr. Rogers to rebut the Examiner's basis of unpredictability that she alleged were supported by his 2001 and 2003 publications. The main point for discussing the Rogers and Barnes 2006 publication, was to state that "inhibition of airway mucus hypersecretion is an unmet clinical need for many patients, especially in COPD,

but also in asthma, CF and bronchiectasis, and that anti-MARCKs drugs merit consideration as potential anti-hypersecretory therapy. Thus just as the Examiner relied upon post-published scientific papers to support unpredictability of using anti-MARCKS therapy, Dr. Rogers wished to point out that he and his colleague believed that such therapy provided another path to reduce the clinical symptom of mucus hypersecretion in patients afflicted by airway diseases.

The Examiner additionally takes the position that there is no evidence that the mouse model of asthma as used in the Parikh Declaration (previously submitted) would be predictive of the efficacy of the MANS peptide or fragments for the treatment of the full scope of diseases encompassed by the claims. In response to the Examiner's position, applicants submit a further clarifying declaration by Dr. Indu Parikh (Attachment B) that provides further explanation regarding the "mouse model of asthma" phrase used in the publications and by Dr. Parikh in his previously submitted declaration. Specifically, Dr. Parikh states that the phrase "mouse model of asthma" is merely a historical term to identify this model because the first publication by Eum studied bronchial hyperreactivity and airway eosinophilia, which are both characteristics of asthma. Dr. Parikh considers that this model is relevant for studying airway mucus hypersecretion and the effect of the N-terminal myristoylated peptides disclosed in the present invention on airway mucus hypersecretion. Further, the mouse model generates a mucus hypersecretory phenotype upon which the peptides are tested and therefore, this model is useful for studying other diseases characterized by the symptom of mucus hypersecretion and bronchial hyperreactivity.

Similarly, Dr. Roger's declaration (Attachment A), attached herewith, declares that the "mouse model of asthma" is a well known model that is useful for studying the effect of treatments on the symptom of mucus hypersecretion in the mouse airways. See paragraph 3 of his attached declaration. He further states that the model is important for the generation of a mucus hypersecretory phenotype in the mouse upon which the effect of a treatment or compositions, such a MANS peptide and/or its fragments may be tested. Dr. Rogers further states that mucus hypersecretion is a major clinical symptom in many respiratory diseases, such as asthma, COPD and CF, and that this model would be useful to study the effect of compounds or treatments on mucus hypersecretion in any disease in which mucus hypersecretion is a major clinical symptom. Similarly, Dr. Parikh in paragraph 5 of his declaration, concurs with Dr.

Rogers' position, that the mouse model is predictive, and thus enabling, for the use of and the MANS peptide and its fragments, to reduce mucus hypersecretion in diseases in which this symptom is a dominant clinical symptom.

Applicants submit that the *in vivo* mouse model provides reliable data to study the inhibition or reduction in mucus hypersecretion as a clinical symptom in a number of respiratory diseases in which mucus hypersecretion is a major clinical symptom. Applicants further submit that they have not made a representation that "MANS peptide would function to modulate all inflammatory mediators associated with the full scope of diseases encompassed by the instant claims." Applicant assert that they have provided evidence that MANS peptide and its fragments inhibit mucus hypersecretion in a mouse model which manifests a mucus hypersecretory phenotype, and therefore has enabled claims that are directed to methods for reducing mucus hypersecretion in the airways of subjects that suffer from diseases in which airway mucus hypersecretion is a dominant clinical finding or symptom, such as pulmonary or respiratory diseases that are associated with mucus hypersecretion by administering MANS peptide or fragments of MANS peptides as defined in the present claims. The specification on page 2, beginning at line 6 of the specification, discloses that: "[h]ypersecretion of mucus contributes to the pathogenesis of a large number of airway inflammatory diseases in both human and non-human animals. Increased mucus secretion is seen in chronic disease states such as asthma, COPD and chronic bronchitis; in genetic diseases such as cystic fibrosis; in allergic conditions (atopy, allergic inflammation); in bronchiectasis; and in a number of acute, infectious respiratory illnesses such as pneumonia, rhinitis, influenza or the common cold."

Thus, applicants submit that they have provided evidence by *in vitro* and *in vivo* data in accepted models to study the effect of compounds/compositions on the treatment of the clinical symptom of mucus hypersecretion in subjects. Therefore, in view of all of the arguments provided above and in our previous responses, in view of Dr. Rogers' and Dr. Parikh's newly submitted declarations as well as their previous declarations, applicants submit that they have provided evidence showing reduction in the clinical symptom of mucus hypersecretion associated with pulmonary diseases characterized by mucus hypersecretion, it is respectfully requested that the Examiner withdraw the lack of enablement rejection of all of the pending claims

3. Obvious-type Double Patenting Rejection

Claims 78-80, 82, 85-89, 91-93, 95-97, 99-109 and 111-115 are provisionally rejected under the judicially created doctrine of obvious-type double patenting as being unpatentable over claims 52-54, 57-67, 70-75 and 85-91 of co-pending U.S. Serial No. 10/802,644 ("the '644 application"). The Examiner alleges that the presently pending set of claims are expressly claiming the same subject matter, although they differ in scope from the claims of the '644 application.

Applicants request that this reinstated rejection be held in abeyance until all of the claims are in condition for allowance. The '644 application is still pending. A review of MPEP Section 804, page-17 of the Rev. 5, August 2006, I., B., 1. where the MPEP instructs the examiner as follows:

> in circumstances where a "provisional" nonstatutory obviousness-type double patenting (ODP) rejection is the only rejection remaining in the earlier filed of the two pending applications, while the later-filed application is rejectable on other grounds, the examiner should withdraw that rejection and permit the earlier-filed application to issue as a patent without a terminal disclaimer.

Therefore, applicants request that the Examiner should withdraw this rejection assuming that she withdraws the rejections discussed above, and as instructed by the MPEP, the ODP rejection should be withdrawn and this application should be allowed to issue. If the Examiner has not withdrawn all of the rejections in the present application, then this rejection should be held in abeyance until all of the rejections are withdrawn.

CONCLUSION

In view of the remarks and supporting documents presented herein and the information provided at the interview with the Examiner, Applicants respectfully submit that the claims define patentable subject matter. If, in the opinion of the Examiner, a telephonic conference would expedite the examination of this matter, the Examiner is invited to call the undersigned attorney at (919) 854-1400.

It is not believed that an extension of time and/or additional fee(s)—including fees for net addition of claims—are required, beyond those that may otherwise be provided for in documents accompanying this paper. In the event, however, that an extension of time is necessary to allow

consideration of this paper, such an extension is hereby petitioned under 37 C.F.R. §1.136(a). Any additional fees believed to be due in connection with this paper may be charged to our Deposit Account No. 50-0220.

Respectfully submitted,

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Enclosures:

Rule 132 Declaration of Duncan F. Rogers, Ph.D.
Rule 132 Declaration of Indu Parikh, Ph.D.

Doc. 553538